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Prevalence of cystic echinococcosis in Iran: a systematic review and meta-analysis

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Abstract

As a significant zoonosis, cystic echinococcosis (CE) is endemic in some parts of the world, such as the Middle East. There are studies on the prevalence of this infection in animal and human reservoirs in Iran; hence, we conducted this meta-analysis to elucidate the prevalence of CE in Iran. English (PubMed, Scopus, Web of Science, Science Direct and Google Scholar) and Persian (Magiran, Iran Medex, Iran Doc and SID) databases were explored. In the case of definitive, animal and human intermediate hosts, 37, 90 and 33 studies, respectively, have been included in the current review from January 1990 to December 2015. According to outcomes of the heterogeneity test, either Der Simonian and Laird's random-effects method or Mantel-Haenszel's fixed-effects method were employed to pool the estimations. The pooled prevalence of *Echinococcus granulosus* infection in definitive hosts was calculated as 23.6% (95% confidence interval (CI) = 17.6–30.1%). The weighted prevalence of animal and human hydatidosis was calculated as 15.6% (95% CI = 14.2–17.1%) and 4.2% (95% CI = 3.0–5.5%), respectively. Meanwhile, most cases of human hydatidosis were in southern Iran, with a prevalence of 5.8% (3.2–9.2%). In terms of human hydatidosis, more infections were found in rural regions, and mostly in female individuals. Egger's regression test revealed publication bias, with a remarkable impact on total prevalence of the infection in animal intermediate hosts ($P < 0.001$), while it was not significant in human hosts ($P = 0.4$) and definitive hosts ($P = 0.3$). According to the weighted estimated prevalence of cystic echinococcosis and its financial burden, implementing appropriate control programmes should be compulsory to decrease the burden of the disease in Iran.

Introduction

Zoonotic diseases are infections that are transmitted among vertebrate animal populations and human societies (Carmena & Cardona, 2014). About one-fifth of zoonoses belong to parasitic infections (Torgerson & Macpherson, 2011). Cystic echinococcosis (CE) is a zoonotic neglected

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tropical disease caused by larval stages (metacestodes) of *Echinococcus granulosus*, the smallest cestode of medical importance and the most common reason for contagion in production animals (Cardona & Carmena, 2013). Echinococcosis is a cyclozoonosis that employs two vertebrate hosts to maintain its life cycle (Cardona & Carmena, 2013; Khademvatan *et al.*, 2013). It mostly occurs as a domestic cycle in cattle- and sheep-raising countries, although a sylvatic cycle among wild carnivore/wild herbivore populations also exists (Cardona & Carmena, 2013; Carmena & Cardona, 2014). Being in the small intestine of canids (definitive hosts), adult worms lay eggs or detach gravid proglottids, which are excreted with the faeces and contaminate the environment, such as grazing pastures; infection of domestic and wild ungulates (intermediate hosts) following ingestion of eggs would then occur by chance. In the intermediate hosts, metacestodes frequently migrate to the liver and lung parenchyma and develop into hydatid cysts (Cardona & Carmena, 2013). Humans are considered to be dead-end intermediate hosts for unilocular echinococcosis. Disease consequences vary from asymptomatic to development of hydatid cysts in the liver, lung and any other parts of the body (McManus *et al.*, 2003). The annual global occurrence of this parasitic complication ranges between 1 and 200 cases per 100,000 individuals (Pawlowski *et al.*, 2001). Furthermore, in various medical centres of Iran, 1.18–3 cases per 100,000 persons have been identified during surgical operations (Fasihi Harandi *et al.*, 2012). CE has been proved to be an important human and animal health concern in many rural regions of western and central Asia, China, Australia, North and East Africa, the Mediterranean territory and South America (Jenkins *et al.*, 2005; Jenkins, 2006; Magambo *et al.*, 2006; Moro & Schantz, 2006a; Romig *et al.*, 2006; Sadjjadi, 2006; Wang *et al.*, 2008; Dakkak, 2010; McManus, 2010; Romig *et al.*, 2011).

There is an inextricable link among human health, animal and environmental health. This association is well-represented by revitalization of infectious zoonoses such as CE in recent years, which accounts for a major worldwide burden. So, characterization of CE prevalence among animal species involved in the transmission cycle is of utmost medical and veterinary importance. Up to now, there have been many research papers on the prevalence of CE in animal hosts in Iran, but the lack of collective data on this subject has led us to design a systematic review and meta-analysis in the country.

Methods

Study area

Covering a wide area in the Middle East (1,648,195 km²), Iran is the 18th largest country worldwide, with a population of approximately 80 million in 2015, located between 25°3' and 39°47'N, and 44°5' and 63°18'E, and bordering Iraq and Turkey in the west, Afghanistan and Pakistan in the east, the Persian Gulf and Oman Sea in the south, as well as Azerbaijan, Armenia and Turkmenistan in the north. Except for a small region on the margin of the Caspian Sea coast with a considerable annual rainfall and covered by dense vegetation, the general climate of Iran is hot and dry, forming the Iranian plateau. It is

one of the world's most mountainous countries, its landscape dominated by rugged mountain ranges that separate various basins or plateaux from each other. The populous western part is the most mountainous, with ranges such as the Caucasus, Zagros and Alborz Mountains. Lower temperatures, severe winters and heavy snowfalls exist in the Zagros basin, while in the central and eastern basins there is an arid climate because of high-altitude mountain ranges in the western and northern parts. These mountain ranges are so high that rain clouds cannot reach the central and eastern basins. Annual precipitation is 680 mm in the eastern part of the plain and more than 1700 mm (66.9 inches) in the western part (<https://en.wikipedia.org/wiki/Iran>).

Search strategy

In order to appraise the prevalence of cystic echinococcosis in Iran, we conducted a systematic review depending on English and Persian online-released literature. The search procedure was performed in five English databases (PubMed, Scopus, Web of Science, Science Direct and Google Scholar) and four Persian databases (Magiran, Iran Medex, Iran Doc and Scientific Information Database) from January 1990 to December 2015 and the medical subject headings (MeSH) terms used for this review were as follows: '*Echinococcus granulosus*', 'Echinococcosis', 'Hydatid', 'Hydatidic', 'Epidemiology', 'Prevalence' and 'Iran', alone or in combination.

Study selection and data extraction

In accordance with the inclusion criteria, cross-sectional studies on the prevalence of CE in definitive and/or intermediate hosts were included. Two autonomous reviewers carefully read and revisited all included papers. Also, incoherence among studies was obviated by discussion and consensus. A data extraction form was designed on the basis of the kind of animals, infected organs (in the case of intermediate hosts), number of studies and positive cases, as well as geographical region, and was used for the accurate information needed. Meanwhile, two risk factors were considered for cases of human echinococcosis, i.e. place of residence and gender. We performed a current meta-analysis according to PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analysis) (Moher *et al.*, 2010).

Meta-analysis

The meta-analysis procedure was performed as described previously (Foroutan-Rad *et al.*, 2016a, b; Foroutan *et al.*, 2017; Khademvatan *et al.*, 2017). Briefly, we estimated the prevalence and 95% confidence interval (CI) of animal echinococcosis for every study that was included. The findings of the meta-analysis were represented by a forest plot diagram, which shows estimates of prevalence and their respective CIs of individual studies with the summary measure. Cochran's *Q* and *I*² statistics were used for evaluation of heterogeneity and inconsistency, respectively. In addition, small study effects and publication bias were calculated using funnel plot diagrams based on Egger's regression test. According to outcomes of the heterogeneity test,

either Der Simonian and Laird's random-effects method or Mantel-Haenszel's fixed-effects method were employed to pool the estimations. Furthermore, studies were categorized in terms of geographical areas (north, east, west, south and centre) of Iran and total prevalence was appraised in five different regions.

Results

Definitive hosts

Based on the review of literature and within the frame of inclusion criteria, 37 out of 5363 records on the prevalence of CE in definitive hosts qualified for this systematic review and meta-analysis (fig. 1 and supplementary table S1).

Table 1 illustrates the findings obtained from the literature search as well as specifications of included studies. It shows the number of canids that were tested in terms of echinococcosis from 1990 until 2015 in various geographical foci of the country (table 1).

The calculated total prevalence of *Echinococcus* infection in definitive hosts was 23.6% (95% CI = 17.6–30.1%). Most canids were found to be infected in the south of Iran, 36.2% (95% CI = 27.0–46.1%), but the fewest cases of infection were detected in the east, 15.3% (95% CI = 8.0–24.1%) (table 2). Publication bias was detected using Egger's

regression test, but didn't have a significant impact on total prevalence estimates in definitive hosts ($P = 0.31$) (table 2).

Meta-regression results showed that there is a statistically significant correlation between total prevalence and both year of studies and sample size ($P = 0.04$ for both) (figs 2 and 3).

Animal intermediate hosts

In total, 90 studies in the field of CE prevalence in animal intermediate hosts were gathered (fig. 1 and supplementary table S2). Database results, number of studies and positive cases are summarized in table 3.

The total prevalence of infection in animal intermediate hosts was assessed as 15.6% (95% CI = 14.2–17.1%). In herbivores, the highest and lowest prevalence rates were observed in the north, 20.2% (95% CI = 13.7–27.7%), and in central Iran, 11.0% (95% CI = 7.4–15.0%), respectively (table 4). Egger's regression test revealed statistically very significant publication bias ($P < 0.001$) (table 4).

In compliance with the meta-regression, there was a remarkable relationship between weighted prevalence and sample size ($P = 0.050$), although prevalence didn't show any substantial correlation with year of studies ($P = 0.29$) (figs 4 and 5).

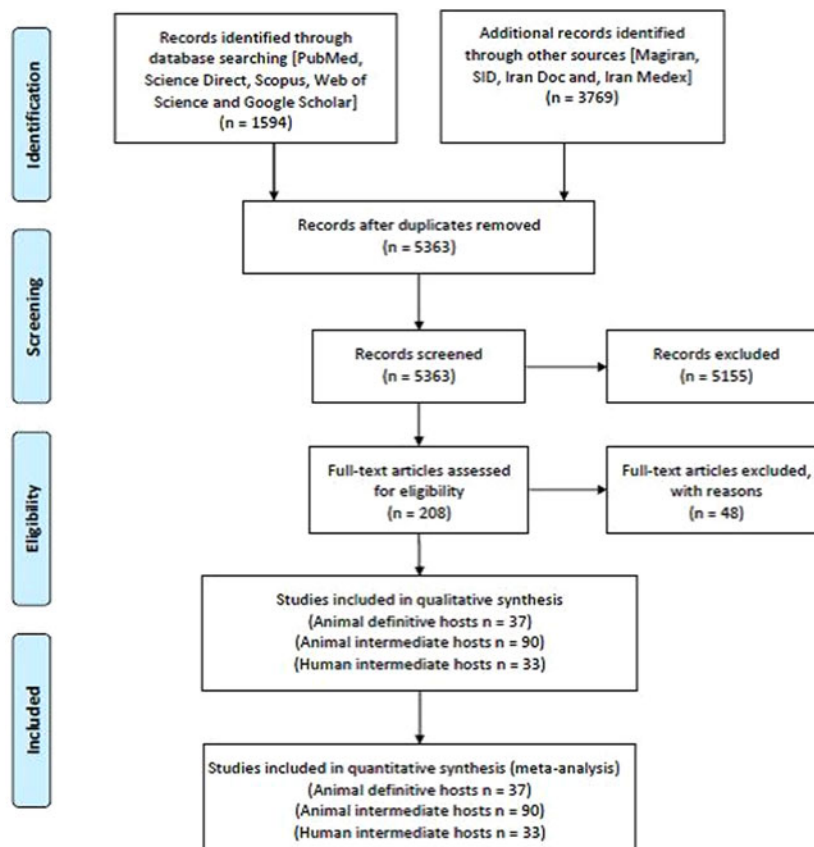


Fig. 1. Flowchart describing the study design process.

Table 1. Results of included studies for definitive hosts.

Host	No. of studies	No. of individuals (<i>n</i>)	No. of positive animals (<i>n</i>)	Prevalence (95% CI)
Dogs	31	10,696	1179	8.8% (8.1–11.9)
Fox	9	399	118	14.9% (0.2–41.5)
Jackal	8	259	37	10.6% (0.6–30.2)
Wolf	3	12	5	39.0% (4.8–79.0)

Table 2. Geographical distribution and prevalence of included studies for definitive hosts.

Region	No. of studies	Prevalence (95% CI)	<i>I</i> ² %	Heterogeneity test		Egger test	
				<i>Q</i>	<i>P</i>	<i>t</i>	<i>P</i>
North	5	25.2% (11.6–41.8)	93.29	59.61	<0.001	1.66	0.856
South	1	36.2% (27.0–46.1)					
Centre	7	34.5% (24.3–45.6)	90.82	65.37	<0.001	2.04	0.278
West	16	21.9% (10.9–35.5)	98.09	786.45	<0.001	−0.35	0.731
East	8	15.3% (8.0–24.1)	93.81	113.01	<0.001	1.24	0.039
Overall	37	23.6% (17.6–30.1)	97.64	1524.69	<0.001	1.03	0.310
Test for heterogeneity between sub-groups:				31.76	<0.001		

Human intermediate hosts

In this section, 33 studies were included (fig. 1 and supplementary table S3). Requisite data were extracted and studies were evaluated in terms of residence and gender risk factors (table 5). More people were infected in rural territories, with a prevalence of 4.1% (95% CI = 1.6–7.8%), than in urban areas. Additionally, mostly females were affected with CE, 4.5% (95% CI = 2.9–6.5%). However, prevalence was not significantly associated with residence or gender ($P = 0.172$; $P = 0.718$) (table 5 and supplementary tables S4 and S5).

The overall prevalence of cystic echinococcosis in human hosts of Iran was calculated as 4.2% (95% CI = 3.0–5.5%). Geographically, the highest prevalence was found in the south, with 5.8% (95% CI = 3.2–9.2%), while the lowest prevalence was appointed to the central regions of the

country, with 2.2% (95% CI = 1.3–3.4%) (table 6). Based on Egger's regression, publication bias did not have a considerable effect on total prevalence in human hosts ($P = 0.4$) (table 6).

Meta-regression between prevalence and both sample size and year of studies showed no significant correlation ($P = 0.424$; $P = 0.994$) (figs 6 and 7).

Discussion

This meta-analysis deals with the prevalence of CE in animal and human populations of Iran. With a synanthropic life cycle among dogs and domestic livestock, *E. granulosus sensu lato* infection has been distributed around the globe. Data from various provinces of Iran were acquired from online documented literature. Altogether, we searched

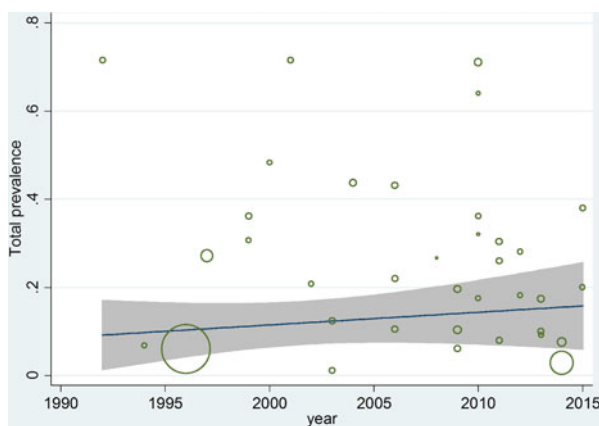


Fig. 2. Meta-regression plot of prevalence of *Echinococcus granulosus* in definitive hosts, based on year of studies.

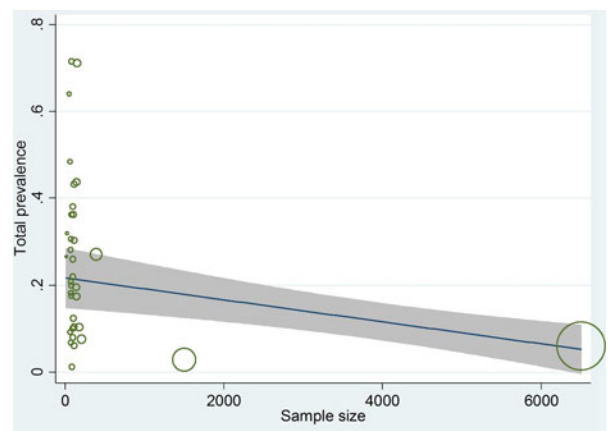


Fig. 3. Meta-regression plot of prevalence of *Echinococcus granulosus* in definitive hosts, based on sample size.

Table 3. Results of included studies for animal intermediate hosts.

Host	No. of studies	No. of individuals (<i>n</i>)	No. of positive animals (<i>n</i>)	Prevalence (95% CI)
Cattle	55	2,869,718	260,592	8.8% (8.1–9.7)
Sheep	60	14,466,454	792,307	5.9% (4.9–7.1)
Goat	50	3,404,007	195,033	6.4% (5.6–7.7)
Buffalo	16	91,811	16,953	16.5% (14.2–18.6)
Camel	13	2938	920	32.7% (23.7–42.3)
Donkey/boar	3	132	9	6.8% (0.6–17.5)

Table 4. Geographical distribution and prevalence of included studies for animal intermediate hosts.

Region	No. of studies	Prevalence (95% CI)	<i>I</i> ² %	Heterogeneity test		Egger test	
				<i>Q</i>	<i>P</i>	<i>t</i>	<i>P</i>
North	11	20.2% (13.7–27.7)	99.99	327151.65	<0.001	7.51	0.664
South	8	18.1% (12.6–24.3)	99.97	25566.43	<0.001	7.77	0.281
Centre	15	11.0% (7.4–15.0)	99.96	36315.12	<0.001	1.94	0.628
West	42	16.8% (14.8–18.8)	99.97	120877.5	<0.001	13.16	<0.001
East	14	13.2% (10.1–16.8)	99.55	126053.53	<0.001	2.54	0.091
Overall	90	15.6% (14.2–17.1)	99.98	597601.37	<0.001	5.03	<0.001
Test for heterogeneity between sub-groups:				10.775	0.029		

nine databases for related articles. In the case of carnivore definitive hosts of CE, 37 papers were found for CE. The estimated total prevalence of infection in definitive hosts was calculated as 23.6% (95% CI = 17.6–30.1%). The gold-standard experiment for detecting infection in canine species is post-mortem examination (intestinal scraping) or sedimentation, while copro-antigen enzyme-linked immunosorbent assay (ELISA) is the method of choice in mass-screening studies (Deplazes *et al.*, 1992; Eckert, 2003; Duscher *et al.*, 2005; Barnes *et al.*, 2012). There have been many studies on the prevalence of canine CE globally. In Africa, very high rates of infection have been detected, particularly in the northern and eastern regions, ranging from 3% in Tunisia to 66% in Uganda (Lahmar *et al.*, 2008; Inangolet *et al.*, 2010). Also, countries neighbouring Iran show a relatively heavy worm burden in dogs, with 49.5%

in Iraq (Saeed *et al.*, 2000), 29.5% in Jordan (Al-Qaoud *et al.*, 2003), 28.2% in Kazakhstan (Stefanic *et al.*, 2004), 20.1% in Uzbekistan (Torgerson *et al.*, 2006), 19% in Kyrgyzstan (Ziadinov *et al.*, 2008) and 15.2% in Tajikistan (Torgerson *et al.*, 2006). The range limits of rates of infection in Europe and the Americas are between 0.2–77.1% and 1.8–79.2%, respectively, and may reach rates greater than even 100% in Australia (Carmena & Cardona, 2013). Three groups of risk factors contribute to disease dispersion in dogs, including biological (age of dog, worm burden and immunity), environmental (climate variations) and human behavioural elements (dog management and principles of slaughtering). Two outcomes are expected from appraising the prevalence and mean abundance of CE infection in carnivorous hosts: (1) to carefully monitor the control programmes; and (2) to evaluate the propagation, dynamics

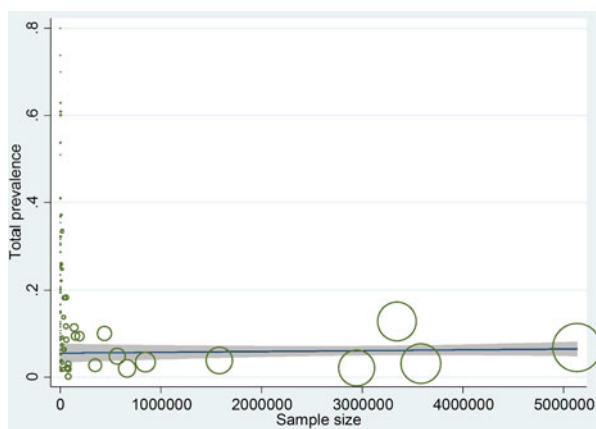
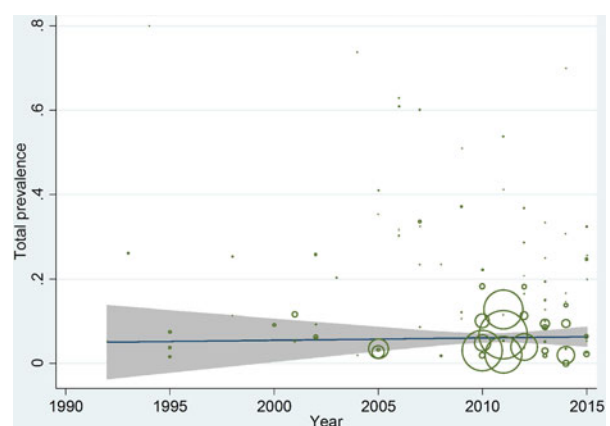
Fig. 4. Meta-regression plot of prevalence of *Echinococcus granulosus* in animal intermediate hosts, based on sample size.Fig. 5. Meta-regression plot of prevalence of *Echinococcus granulosus* in animal intermediate hosts, based on year of studies.

Table 5. Results of included studies for human hosts.

Risk factors	No. of studies	Category	Total individuals	Positive cases	Overall prevalence (%)	P value
Residence	9	Urban	6774	133	2.1% (1.1–3.4)	0.172
		Rural	5464	191	4.1% (1.6–7.8)	
Gender	20	Male	11,680	643	4.0% (2.4–6.0)	0.718
		Female	16,284	1032	4.5% (2.9–6.5)	

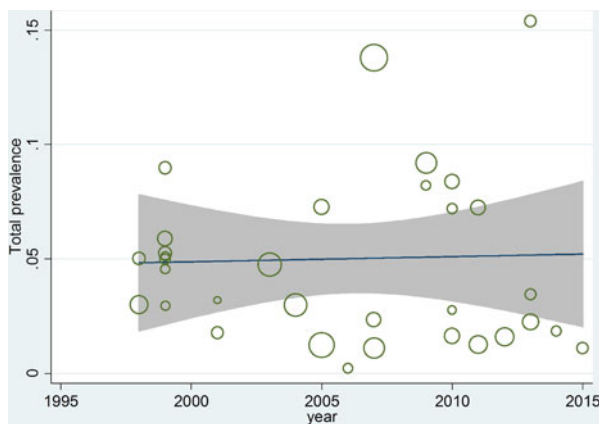
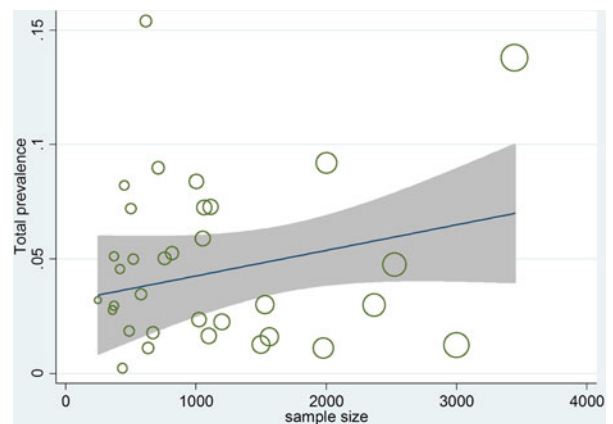
Table 6. Geographical distribution and prevalence of included studies for human hosts.

Region	No. of studies	Prevalence (95% CI)	I^2 %	Heterogeneity test		Egger test	
				Q	P	t	P
North	9	4.4% (2.3–7.0)	96.24	212.62	<0.001	-1.04	0.46
South	4	5.8% (3.2–9.2)	90.04	30.13	<0.001	-0.91	0.69
Centre	8	2.2% (1.3–3.4)	90.09	70.67	<0.001	-0.27	0.69
West	12	5.0% (2.7–8.1)	98.49	727.79	<0.001	-0.30	0.86
Overall	33	4.2% (3.0–5.5)	97.24	1160.19	<0.001	-0.45	0.41
Test for heterogeneity between sub-groups:				9.145	0.027		

of transmission and status of human infection in a particular region (Craig *et al.*, 2003; Romig *et al.*, 2011; Barnes *et al.*, 2012).

Among 90 records obtained from the literature review, weighted prevalence was evaluated as 15.6% (95% CI = 14.2–17.1%) in animal intermediate hosts. Infection identification was similar to that of definitive hosts, relying mostly upon animal post-mortem inspection in abattoirs (Carmena & Cardona, 2013). According to scientific reports in Africa, highest prevalences of hydatidosis in sheep (0.2–68%), goats (0.2–65%) and camels (1.9–61%), were recorded (Bardonnnet *et al.*, 2002; Njoroge *et al.*, 2002; Sissay *et al.*, 2008). In Asia, the greatest rate of infection among production animals was found in sheep intermediate hosts (0.1–82.6%) (Yu *et al.*, 2008; Pednekar *et al.*, 2009); furthermore, among Iran's neighbours, CE prevalence in sheep ranged from 7.5% in Pakistan (Latif *et al.*,

2010) to 64.2% in Kyrgyzstan (Torgerson *et al.*, 2009), while cattle and goat infections were 1.8–45.5% and 5.5–11.1%, respectively (Torgerson *et al.*, 2006; Latif *et al.*, 2010; Guo *et al.*, 2011). In Europe, sheep (0–75%), and to a lesser extent cattle (0–41.5%) and goats (0–25.7%), were more involved and are considered to be the main intermediate hosts (Varcasia *et al.*, 2006, 2007; European Food Safety Authority, 2015). The same situation exists in the Americas (Cardona & Carmena, 2013; Carmena & Cardona, 2013). Many risk factors may be involved in disease spatial distribution, such as farm hygiene practices and breeding conditions, environmental elements and strain/genotype of hydatid cysts, as well as socio-cultural beliefs (Eckert & Deplazes, 2004). Hydatid infection in livestock not only leads to the need to regulate disposal of infected viscera and dead animals, and to international restrictions on export of infected products,

Fig. 6. Meta-regression plot of prevalence of *Echinococcus granulosus* in human hosts, based on year of studies.Fig. 7. Meta-regression plot of prevalence of *Echinococcus granulosus* in human hosts, based on sample size.

but the infection also detracts from the quality and quantity of livestock products (milk, meat, wool and feathers) and reduces birth rates. Hence, requisite control measures should be taken into account (Torgerson, 2003).

In total, 33 articles related to humans as the aberrant intermediate hosts of hydatidosis were gathered, resulting in a 4.2% (95% CI = 3.0–5.5%) pooled prevalence of hydatid cyst infection. The infection rate was higher in rural regions, with 4.1% (95% CI = 1.6–7.8%); we also found that 4.5% (95% CI = 2.9–6.5%) of women were infected, having more positive cases than men. The greatest rate of prevalence is frequently correlated with temperate regions. Human hydatidosis is an endemic infection in some parts of the world, including in Asia, Australia, South America, North Africa and the Mediterranean littoral (Kilic *et al.*, 2003; Moro & Schantz, 2006b, 2009; Yang *et al.*, 2006). In these regions, the incidence rate of human CE was reported to be fewer than 50 cases/100,000 inhabitants (Mandal & Mandal, 2012). Accordingly, in a recent systematic review (Budke *et al.*, 2013), annual rates of incidence were limited to 0–32 cases/100,000 individuals in hospital-based studies, representing an optimistic hospitalization estimation of 32 cases every year. Besides, the prevalence of hydatid infection reached 1–7% in cross-sectional community-based studies. Consistent with our result, women showed elevated CE prevalence rates (prevalence proportion ratio: 1.35) in this review and hence are considered more prone to infection than men, probably due to traditional household tasks in endemic lands, such as dealing with dogs, gardening and food preparation. Based on Budke *et al.* (2013), with regard to imaging techniques, the three top prevalence rates of hepato-pulmonary CE were assigned to China.

Our findings about the prevalence of cystic echinococcosis in Iran were affected by some limitations, comprising: (1) lack of a modulus question form to obtain needed information in most human studies; (2) lack of an appropriate, identical-examination method with high specificity and sensitivity; and (3) absence of studies in some regions of the country. These restrictions may bias the reported epidemiologic aspects of CE infection.

In Iran, it has been estimated that a financial burden of up to US\$232.3 million per annum is inflicted by CE, divided into human and animal cases with losses of US\$93.39 million and US\$132 million, respectively. Also, the surgical cost of human cases was estimated at US\$1539 (Fasihi Harandi *et al.*, 2012). Disease control, reduction of infection prevalence in animals, and hence interrupting the transmission cycle, are not only decisive practices to lower the incidence rate of human hydatidosis, but also lead to an economically improved society. Therefore, given the information extracted from the current systematic review and meta-analysis, safety precautions and management programmes in cases of animal and human cystic echinococcosis should be devised.

Supplementary material

To view supplementary material for this article, please visit <https://doi.org/10.1017/S0022149X17000463>

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Authors' contributions

S.K. conceived the study; S.K. and H.K. designed the study protocol; M.F. and S.K. searched the literature; P.K. and S.A. extracted the data; H.K. analysed and interpreted the data; H.M. wrote the manuscript; S.K., H.M. and A.A. critically revised the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical standards

This study was approved by the Ethical Committee of Urmia University of Medical Sciences, Urmia, Iran (no.: Ir.UMSU.rec.1395.242).

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